Anemia, Fanconi

Synonyms, Key Words, and Related Terms: Fanconi anemia, FA, constitutional aplastic anemia, bone marrow failure, aplastic anemia, leukemia, myelodysplastic syndrome, liver adenoma, hepatoma, radial ray anomalies, poor growth, genitourinary problems, short stature, skin pigmentation, café au lait spots, petechiae, bruises, bruising, pallor, fatigue, infections, thumb anomalies, thumb and radial anomalies, abnormal male gonads, microcephaly, eye anomalies, structural renal defects, low birth weight, developmental delay, abnormal ears abnormal hearing, Estren Dameshek Fanconi anemia

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INTRODUCTION

Background: Fanconi anemia (FA) is the most frequently reported of the rare inherited bone marrow failure syndromes, with more than 1200 cases reported in the medical literature. In 1927, Fanconi first reported 3 brothers with pancytopenia and physical abnormalities. Subsequent cases were diagnosed clinically because of the combination of aplastic anemia

and various characteristic physical anomalies (see Physical).

In the early 1960s, several groups observed that cultured cells from patients with FA had increased numbers of chromosome breaks, and later it was found that the breakage rate was specifically increased by the addition of DNA cross-linkers, such as diepoxybutane (DEB) or mitomycin C (MMC). This led to the identification of FA patients with aplastic anemia without birth defects and the diagnosis of FA in patients with abnormal physical findings without aplastic anemia. Furthermore, in cultured FA cells, cell cycle arrest in gap 2/mitosis (G2/M) occurs at lower concentrations of clastogens than in normal cells. This observation has led to flow cytometry–based screening tests used at some centers.

Most recently, the advent of molecular diagnostics has further improved the specificity of FA diagnosis (see Other Tests). FA comprises approximately 25% of the cases of aplastic anemia seen at large referral centers. Approximately 25% of known FA patients do not have major birth defects.

Pathophysiology: FA is an autosomal recessive disease; thus, each FA patient is homozygous or doubly heterozygous for mutations in one of the 8 different genes known to be responsible for FA. The genes are termed *FANCA* through *FANCG,* and genes have been cloned for *FANCA, FANCC, FANCD2, FANCE, FANCF,* and *FANCG*.

The FA proteins A, C, E, F, and G appear to form a nuclear complex, which leads to ubiquitination of the D2 protein, which may be involved in DNA damage response mechanisms. The widely variant FA phenotype may depend on whether the mutation is null or leads to a partially functional gene product rather than the specific gene that is involved. The specific role of mutations in the FA genes in the pathogenesis of birth defects, bone marrow failure, or oncogenesis is not yet clear.

Frequency:

- **In the US:** The carrier frequency is estimated to be approximately 1 per 300 population, leading to an expected birth rate of approximately 1 per 360,000 population. Among Ashkenazi Jews, the carrier frequency is approximately 1 per 90 population, with a projected birth rate of 1 per 30,000 population.

- **Internationally:** The carrier frequencies are similar to those in the United States, depending on the population. The birth rate in Afrikaners in South Africa is 1 in 22,000 population, with an expected heterozygote frequency of 1 per 77 population.

Mortality/Morbidity:

- The major cause of death in FA is bone marrow failure, followed in frequency by leukemia and solid tumors. The projected median survival from all causes for more than 1000 cases reported in the literature is age 20 years, although this has improved to 30 years in the cases reported in the most recent decade.

- Bone marrow failure usually appears in childhood, with petechiae, bruising, and hemorrhages caused by thrombocytopenia, pallor and fatigue from anemia, and infections due to neutropenia. More than 90% of patients with FA develop pancytopenia caused by aplastic anemia, which is often fatal. Leukemia was reported in approximately 10% of patients and myelodysplastic syndrome in about 6% of patients, primarily in teens and young adults, some of whom may not have had a preceding aplastic anemia phase. Solid tumors were reported in close to 10%, often in young adults who may never have had aplastic anemia. The most common tumors are liver adenomas and hepatomas, primarily in patients who had aplastic anemia that was treated with oral androgens. The other types of solid tumors occur in young adults and involve primarily the head and neck, esophagus, and gynecologic areas. Oral cancers also have been reported in patients with FA who have received a bone marrow transplantation, which may increase the risk of these cancers.

Race: FA has been reported in all races, although “founder” effects exist, which result in higher carrier frequencies in Ashkenazi Jews and Afrikaners (see Frequency).

Sex: The male-to-female ratio in the literature cases is 1.2:1, although equal numbers are expected in autosomal

recessive disease.

Age: FA has been diagnosed in patients from birth to age 48 years, with a median of age 7-8 years. Individuals with birth defects (see Physical) are diagnosed at younger ages than persons without birth defects.

CLINICAL

History: Patients with FA with characteristic birth defects, such as radial ray anomalies, poor growth, or genitourinary problems, often are treated by a variety of medical specialists during infancy. The diagnosis of FA must first be considered and can only be established if specific tests are ordered. During childhood, short stature and skin pigmentation, including café au lait spots, may become apparent. The first sign of a hematologic problem is usually petechiae and bruises, with later onset of pallor, fatigue, and infections. Because macrocytosis usually precedes thrombocytopenia, patients with typical congenital anomalies associated with FA should at least be evaluated for an elevated erythrocyte mean corpuscular volume. In approximately 25% of patients with FA who have cancer, the diagnosis of leukemia or a tumor preceded the diagnosis of FA.

Physical: About 75% of patients with FA have birth defects, such as altered skin pigmentation and/or café au lait spots (>50%), short stature (50%), thumb or thumb and radial anomalies (40%), abnormal male gonads (30%), microcephaly (25%), eye anomalies (20%), structural renal defects (20%), low birth weight (10%), developmental delay (10%), and abnormal ears or hearing (10%). Literature reports may, however, be biased towards this association because the clinical diagnosis initially was dependent on the combination of aplastic anemia and physical anomalies. Thus, the frequencies may be overestimated.

- Skin - Generalized hyperpigmentation on trunk, neck, and intertriginous areas; café au lait spots, hypopigmented areas
- Body - Short stature, delicate features
- Upper limbs
    - Thumbs - Absent or hypoplastic, supernumerary, bifid, rudimentary, short, low set, attached by a thread, triphalangeal, tubular, stiff, hyperextensible
    - Radii - Absent or hypoplastic (only with abnormal thumbs, ie, terminal defects), absent or weak pulse
    - Hands - Clinodactyly, hypoplastic thenar eminence, 6 fingers, absent first metacarpal, enlarged abnormal fingers, short fingers
    - Ulnae - Dysplastic
- Gonads
    - Males - Hypogenitalia, undescended testes, hypospadias, abnormal or absent testis, atrophic testes, azoospermia, phimosis, abnormal urethra, micropenis, delayed development
    - Females - Hypogenitalia; bicornuate uterus; aplasia of uterus and vagina; atresia of uterus, vagina, ovary
- Other skeletal anomalies
    - Head and face - Microcephaly, hydrocephalus, micrognathia, peculiar face, bird face, flat head, frontal bossing, scaphocephaly, sloped forehead, choanal atresia

- Neck - Sprengel abnormality, short, low hairline, webbed
- Spine - Spina bifida (thoracic, lumbar, cervical, occult sacral), scoliosis, abnormal ribs, sacrococcygeal sinus, Klippel-Feil syndrome, vertebral anomalies, extra vertebrae
- Feet - Toe syndactyly, abnormal toes, flat feet, short toes, clubfoot, 6 toes
- Legs - Congenital hip dislocation, Perthes disease, coxa vara, abnormal femur, thigh osteoma, abnormal legs

- Eyes - Small, strabismus, epicanthal folds, hypertelorism, ptosis, slanted, cataracts, astigmatism, blindness, epiphora, nystagmus, proptosis, small iris
- Ears - Deaf (usually conductive), abnormal shape, atresia, dysplasia, low-set, large, small, infections, abnormal middle ear, absent drum, dimples, rotated, canal stenosis
- Kidneys - Ectopic or pelvic, horseshoe, hypoplastic or dysplastic, absent, hydronephrosis or hydroureter, infections, duplicated, rotated, reflux, hyperplasia, no function, abnormal artery
- Gastrointestinal system: High-arch palate, atresia (eg, esophagus, duodenum, jejunum), imperforate anus, tracheoesophageal fistula, Meckel diverticulum, umbilical hernia, hypoplastic uvula, abnormal biliary ducts, megacolon, abdominal diastasis, Budd-Chiari syndrome.
- Cardiopulmonary system - Patent ductus arteriosus, ventricular septal defect, peripheral pulmonic stenosis, aortic stenosis, coarctation, absent lung lobes, vascular malformation, aortic atheromas, atrial septal defect, tetralogy of Fallot, pseudotruncus, hypoplastic aorta, abnormal pulmonary drainage, double aortic arch, cardiomyopathy
- Other anomalies - Developmental delay, hyperreflexia, Bell palsy, CNS arterial malformation, stenosis of the internal carotid, small pituitary gland

Causes: As described in Pathophysiology, at least 8 genes are involved in the FA pathway. The exact link between mutations and phenotype is not clear, although it does appear that patients who are homozygous for null mutations have more severe FA than those with altered proteins. Various aspects of pathophysiologic research include the following:

- FA cells may be susceptible to damage by oxygen free radicals.
- FA cells have a defect in cell cycle regulation.
- The hematopoietic stem cell is defective in FA.
- A defect in the DNA-damage response pathway exists in FA.

DIFFERENTIALS

Holt-Oram Syndrome
Myelodysplastic Syndrome
Pearson Syndrome
Shwachman-Diamond Syndrome
Thrombocytopenia-Absent Radius Syndrome

Other Problems to be Considered:

Acquired aplastic anemia
Acute myeloid leukemia
Bloom syndrome
Diamond-Blackfan anemia
Dubowitz syndrome
Dyskeratosis congenita
Rothmund-Thomson syndrome
Seckel syndrome
Vertebral, anal, cardiac, tracheal, esophageal, limb (VACTERL) association
Werner syndrome
Immune pancytopenias
In utero viral infections
Teratogens

WORKUP

Lab Studies:

- Complete blood count may reveal trilineage pancytopenia or may only show red blood cells that are macrocytic for age. Thrombocytopenia or leukopenia may precede full-blown aplasia.
- Chromosome breakage usually is examined in short-term cultures of peripheral blood lymphocytes in the presence of DNA cross-linkers, such as DEB or MMC. These agents lead to increased numbers of breaks, gaps, rearrangements, and quadriradii in FA homozygote cells.
- Flow cytometry of FA cells cultured with nitrogen mustard and other clastogens demonstrates an arrest in G2/M.
- Fetal hemoglobin (HbF) may be increased for age as a manifestation of stress erythropoiesis.
- Red cell adenosine deaminase (ADA) is increased in the most patients with Diamond-Blackfan anemia (DBA) but appears to be normal in FA.
- Serum erythropoietin (Ep) levels are increased markedly and higher than expected for the degree of anemia, similar to that observed in DBA. However, levels may be low in patients with impaired renal function.

Imaging Studies:

- Perform a skeletal survey to identify all developmental defects involving bone.
- Obtain an initial ultrasound of abdomen to document size and location of kidneys and perform follow-up ultrasounds annually to monitor for liver tumors or peliosis hepatis.
- Obtain a cardiac ultrasound to evaluate for congenital anomalies.
- Central nervous system magnetic resonance imaging is indicated to identify any structural defects, such as absence of the corpus callosum or cerebellar hypoplasia.

Other Tests:

- Mutations in specific FA genes often can be identified. These tests generally are performed only in research laboratories, with the exception of the relatively common FA mutation found in Ashkenazi Jews (IVS4 +4 A to T). FA lymphocytes are treated with vectors containing normal clones of the known FA genes; correction of chromosome breakage or of impaired growth by a specific vector indicates that the cells have a mutation in that gene. The

specific mutation can be determined by various molecular diagnostic approaches.

Procedures:

- Bone marrow aspirate and biopsy may reveal hypocellularity, loss of myeloid and erythroid precursors and megakaryocytes (with relative lymphocytosis), or full-blown aplasia with a fatty marrow. Signs of myelodysplastic syndrome include dyserythropoiesis (multinuclearity, ringed sideroblasts), dysmyelopoiesis (hyposegmentation, hypogranularity, hypergranularity), and hypolobulated or hyperlobulated megakaryocytes. Presence of a cytogenetic clone in a high and increasing proportion over time may suggest an evolution to leukemia, but this is currently unproven.

- Prenatal diagnosis of FA can be accomplished by demonstration of chromosome breaks in cells obtained in utero from chorionic villus biopsy, amniocentesis, or cord blood (by cordocentesis), or by identification of FA gene mutations in DNA extracted from fetal cells.

- Preimplantation genetic diagnosis has been done using molecular methods, resulting in implantation of an embryo without FA mutations that was human leukocyte antigen (HLA)–matched with the affected FA sister; cord blood from the delivery was used for a hematopoietic stem cell transplantation resulting in the cure of the sister's aplastic anemia.

TREATMENT

Medical Care: Treatment is recommended for significant cytopenias, such as hemoglobin less than 8 g/dL, platelets less than 30,000/mL, or neutrophils less than 500/mL. Although the first line of therapy is stem cell transplantation, androgens, to which approximately 50-75% respond, are used for those in whom transplantation is not an option (see Medication).

Supportive care for symptomatic anemia includes transfusions of packed red blood cells that have been leukodepleted (and are not from family members, to avoid sensitization in case of a future transplantation). Symptomatic thrombocytopenia can be treated with similarly treated platelets; single-donor platelets are preferred, to reduce the incidence of antibody formation. Symptomatic neutropenia usually responds to granulocyte colony-stimulating factor (G-CSF, see Medication). Some clinicians have advocated corticosteroids, which are used to delay growth plate closure in patients treated with androgens and to improve vascular integrity and reduce bleeding.

Hematopoietic stem cell transplantation (bone marrow, cord blood, or peripheral blood stem cells) may cure aplastic anemia and prevent myelodysplastic syndrome or leukemia. It should be considered for those who have an HLA-matched sibling donor (survival rate is >80%). The survival rate after transplantation from alternative donors is still poor (generally <50%); thus, this risky procedure should be reserved for patients who have leukemia or myelodysplasia and do not have HLA-matched related donors and for patients either unable to tolerate or refractory to standard medical treatment.

Surgical Care: Splinting and hand surgery may be indicated for thumb and radial anomalies. Congenital heart defects may require surgery. GI anomalies, such as tracheoesophageal fistulas, also are treated surgically.

Consultations: Patients with specific birth defects or medical problems should be referred to the appropriate consultants (eg, hand surgeon, cardiologist, dermatologist, endocrinologist, gastroenterologist, geneticist).

Activity: Patients with thrombocytopenia should avoid trauma, such as that resulting from contact sports, and should use helmets and padding. Those with anemia should participate in strenuous activities only under supervision and only as tolerated. Those with severe neutropenia need to avoid exposure to people with active infections.

MEDICATION

Drug Category: *Androgenic agents* -- Enhance the production and urinary excretion of erythropoietin in anemias

caused by bone marrow failure and often stimulate erythropoiesis in anemias caused by deficient red cell production. They appear to make hematopoietic stem cells more responsive to differentiation, but the exact mechanism is not clear. The usual agent is oral oxymetholone, a 17-beta-hydroxylated androgen. Although oral androgens have a risk of liver toxicity, they are easier to use in children than parenteral androgens. In the United States, the most frequently used androgen for FA is oxymetholone. The lowest effective dose should be used.

Drug Name	Oxymetholone (Anadrol-50) -- Anabolic and androgenic derivative of testosterone in an oral formulation.
Adult Dose	2-5 mg/kg/d PO
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity; male breast or prostate cancer; metastatic female breast cancer with hypercalcemia; nephrosis or nephrotic phase of nephritis; known or suspected pregnancy; severe liver disease
Interactions	May increase sensitivity to anticoagulants (dosage of an anticoagulant may have to be decreased to maintain the PT at the desired therapeutic level); may increase effects of insulin
Pregnancy	X - Contraindicated in pregnancy
Precautions	Virilization (deepening of the voice, hirsutism, acne, enlargement of genitalia) common and may be irreversible, even after prompt discontinuance of therapy; menstrual irregularities, including amenorrhea, possible; insulin or oral hypoglycemic dosage may need adjustment; may cause suppression of clotting factors II, V, VII, and X; may cause an increase in PT Cholestatic hepatitis, peliosis hepatis, liver tumors, and blood lipid changes that increase the risk of atherosclerosis possible; monitoring includes liver function tests and liver ultrasound examinations

Drug Name	Nandrolone decanoate (Deca-Durabolin) -- A parenteral androgen sometimes is selected because of the lower risk of hepatic tumors. As with oxymetholone, the lowest effective dose should be used.
Adult Dose	1-2 mg/kg/wk IM
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity; male breast or prostate cancer; metastatic female breast cancer with hypercalcemia; nephrosis or nephrotic phase of nephritis; known or suspected pregnancy; severe liver disease
Interactions	May increase sensitivity to anticoagulants (dosage of an anticoagulant may have to be decreased to maintain the PT at the desired therapeutic level); may increase effects of insulin
Pregnancy	X - Contraindicated in pregnancy
Precautions	Virilization (deepening of the voice, hirsutism, acne, enlargement of genitalia) common and may be irreversible, even after prompt discontinuance of therapy; menstrual irregularities, including amenorrhea, also possible; insulin or oral hypoglycemic dosage may need adjustment; may cause suppression of clotting factors II, V, VII and X and an increase in PT

Drug Category: *Antifibrinolytic agents* -- May decrease bleeding, particularly oral mucosal bleeding, in patients with thrombocytopenia by stabilization of thrombi.

Drug Name	Aminocaproic acid (Amicar) -- Competitively inhibits activation of plasminogen to plasmin.
Adult Dose	30 g/d PO/IV in divided doses q3-6h; not to exceed 30 g/d
Pediatric Dose	100-200 mg/kg PO/IV loading dose; followed by 200-400 mg/kg/d PO divided q6h for 7-10 d. Renal impairment: 50 mg/kg/d PO qd

Contraindications	Documented hypersensitivity; hematuria; evidence of active intravascular clotting process; because aminocaproic acid can be fatal in patients with disseminated intravascular coagulation (DIC), differentiate between hyperfibrinolysis and disseminated intravascular coagulation
Interactions	Coadministration with estrogens may cause increase in clotting factors, leading to a hypercoagulable state
Pregnancy	D - Unsafe in pregnancy
Precautions	Decrease dose to 50 mg/kg/d PO qd in severe renal impairment; caution in cardiac or hepatic disease

Drug Category: *Hematopoietic growth factors* -- These factors are glycoproteins that act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation, commitment, and some end cell functional activation.

Drug Name	Filgrastim (G-CSF, Neupogen) -- G-CSF that activates and stimulates production, maturation, migration, and cytotoxicity of neutrophils.
Adult Dose	2-10 mcg/kg SC qd/qod
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity
Interactions	Caution in coadministration with drugs that may potentiate the release of neutrophils (eg, lithium)
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	May cause bone pain, flulike symptoms, nausea, or vomiting; do not dilute to concentrations <5 mcg/mL; do not dilute with saline; potential risk of evolution to leukemia

Drug Name	Epoetin alfa (Epogen, Procrit) -- Stimulates division and differentiation of committed erythroid progenitor cells; induces release of reticulocytes from bone marrow into blood stream.

Adult Dose	100-250 U/kg SC 3 times/wk
Pediatric Dose	Administer as in adults
Contraindications	Documented hypersensitivity (including hypersensitivity to human albumin, hypersensitivity to mammalian cell-derived products); uncontrolled hypertension
Interactions	None reported
Pregnancy	C - Safety for use during pregnancy has not been established.
Precautions	Caution in hypertension, history of seizures, thrombocytosis, chronic hepatic impairment, ischemic vascular disease, or malignant tumors; blood pressure must be monitored

Drug Category: *Glucocorticoids* -- Corticosteroids are used on alternate days to delay the growth acceleration caused by androgens. They also may stabilize endothelial cells, leading to reduced bleeding at a given degree of thrombocytopenia. Some clinicians accept the use of corticosteroids.

Drug Name	Prednisone (Deltasone, Liquid Pred) -- Elicits anti-inflammatory properties and causes profound and varied metabolic effects. Modifies the body's immune response to diverse stimuli.
Adult Dose	5-10 mg PO qod
Pediatric Dose	5 mg PO qod
Contraindications	Documented hypersensitivity; viral, fungal, or tubercular skin infections
Interactions	Coadministration with digoxin may increase digitalis toxicity secondary to hypokalemia; estrogens may increase levels of methylprednisolone; phenobarbital, phenytoin, and rifampin may decrease levels of methylprednisolone (adjust dose); monitor patients for hypokalemia when taking medication concurrently with diuretics
Pregnancy	B - Usually safe but benefits must outweigh the risks.

Precautions	May increase the risk of serious or fatal infection in individuals exposed to viral illnesses, such as chickenpox or measles; hyperglycemia, edema, osteonecrosis, peptic ulcer disease, hypokalemia, osteoporosis, euphoria, psychosis, growth suppression, myopathy, and infections are possible complications

Further Inpatient Care:

- Inpatient care may be needed for complications of bone marrow failure (eg, bleeding, infection). Transfusions may be given as inpatient or outpatient treatment. Hematopoietic stem cell transplantation is currently an inpatient procedure. Hospitalization may be needed for treatment of other complications (eg, leukemia, tumors).

Further Outpatient Care:

- Blood counts are recommended at 3-month intervals or more often as needed. Transfusions of red cells or platelets can be given to outpatients. Annual bone marrow examinations can be outpatient procedures.

Deterrence/Prevention:

- Carrier screening can be offered as part of reproductive counseling for Ashkenazi Jews or Afrikaners, groups in which there is a founder effect and a carrier rate of more than 1/100. In utero prenatal diagnosis is available, and preimplantation genetic diagnosis may be possible as an experimental procedure.

Complications:

- Possible complications include hemorrhages, infections, leukemia, myelodysplastic syndrome, liver tumors, and other cancers.
- Leukemia was reported in more than 100 patients with FA (out of approximately 1200 reported in the literature), of which 95% were acute myeloid leukemias (usually rare in children).
- Myelodysplastic syndrome was reported in approximately 75 patients; many of these patients did not develop leukemia but died from complications of impaired marrow function.
- Liver tumors occurred in more than 30 patients, often in the context of aplastic anemia or other tumors, and usually were not malignant (although two thirds were histologically hepatomas, and the rest were adenomas).
- More than 70 solid tumors were reported in more than 60 patients. In order of frequency, these tumors were tumors of the oropharynx, esophagus, vulva, brain, skin (nonmelanoma), cervix, breast, kidney, lung, lymph nodes (lymphoma), stomach, and colon, followed by osteogenic sarcoma and retinoblastoma. At least 10 oral cancers have been reported in FA patients following bone marrow transplantation.

Prognosis:

- Treatment of aplastic anemia with medications, supportive use of blood products, and stem cell transplantation increases the life expectancy beyond the projected median of 30 years. Cancer prevention and screening to identify

early malignancies may reduce the mortality rate from cancer. Although many patients with FA are short and have skeletal anomalies, intelligence is usually normal, and education and career planning should be encouraged.

Patient Education:

- Educate patients and their families regarding behaviors with risk of bleeding, as well as maintenance of hygiene to reduce infections. Emphasize the need to comply with medications and transfusions. Educate patients and their families about cancer prevention (eg, smoking, drinking, diet, life style) and cancer screening (eg, bone marrow, oropharyngeal, and gynecological examinations).
- The genetic basis of FA needs to be explained, and apparently unaffected siblings should be tested for FA homozygosity. Provide genetic counseling to the parents and other carriers or potential carriers with regard to the risk of recurrence. Discuss phenotypic variability within a family.

MISCELLANEOUS

Medical/Legal Pitfalls:

- Failure to diagnose aplastic anemia or leukemia may lead to delays in treatment. The diagnosis of FA must be made to avoid the inappropriate use of immunosuppressive therapy for aplastic anemia, the use of toxic levels of chemotherapy in leukemia, or toxic types of preparation for a stem cell transplantation. FA is one of the few forms of aplastic anemia in which the response to androgens is more than 50%.
- Related transplant donors must be proven not to have FA in order for a transplantation to succeed.
- Patients who have tumors that are characteristic of FA but who present without the usual risk factors for those tumors need to be screened for FA (eg, head and neck cancer in a 20-year-old woman who does not smoke or drink).

Special Concerns:

- The diagnosis of FA is not made using routine laboratory tests, but it must be considered and tested for by chromosome breakage or mutation analysis. Siblings who do not apparently have FA need to be screened for occult FA.

PICTURES

Caption: Picture 1. A 3-year-old patient with Fanconi anemia. Note the multiple birth defects, including short stature, microcephaly, microphthalmia, epicanthal folds, dangling thumbs, site of ureteral reimplantation, congenital dislocated hips, and rocker bottom feet. (Alter BP, Young NS. The bone marrow failure syndromes. In: Nathan DG, Oski FA, eds. *Hematology of Infancy and Childhood,* 4th ed. Philadelphia, PA: W.B. Saunders, Inc., 1993: pp. 216-316.)


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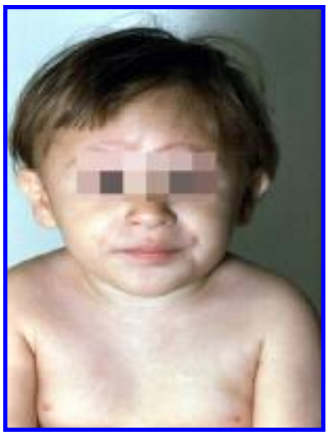
Picture Type: Photo

Caption: Picture 2. Close-up of the face of 3-year-old patient with Fanconi anemia (same patient as in Image 1). (Alter BP, Young NS. The bone marrow failure syndromes. In: Nathan DG, Oski FA, eds. *Hematology of Infancy and Childhood,* 4th ed. Philadelphia, PA: W.B. Saunders, Inc., 1993: pp. 216-316.)



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Picture Type: Photo

Caption: Picture 3. Café au lait spot and hypopigmented area in a 3-year-old patient with Fanconi anemia (same patient as in Images 1 and 2). (Alter BP, Young NS. The bone marrow failure syndromes. In: Nathan DG, Oski FA, eds. *Hematology of Infancy and Childhood,* 4th ed. Philadelphia, PA: W.B. Saunders, Inc., 1993: pp. 216-316.)

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Picture Type: Photo

Caption: Picture 4. Thumbs attached by threads on a 3-year-old patient with Fanconi anemia (same patient as in Images 1, 2, and 3). (Alter BP, Young NS. The bone marrow failure syndromes. In: Nathan DG, Oski FA, eds. *Hematology of Infancy and Childhood,* 4th ed. Philadelphia, PA: W.B. Saunders, Inc., 1993: pp. 216-316.)

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Picture Type: Photo

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